RDT&E BUDGET ITEM JUSTIFICATION SHEET (R-2 Exhibit)									DATE February 2000
APPROPRIATION/BUDGET ACTIVITY RDT&E, Defense Wide/BA 2							R-1 ITEM NOMENCLATURE Medical Technology PE 0602787D8Z		
COST*(In Millions)*	FY 1999	FY 2000	FY 2001	FY 2002	FY 2003	FY 2004	FY 2005	Cost to Complete	Total Cost
Total Program Element (PE) Cost	9.119	8.875	8.680	8.921	9.130	9.289	9.423	Continuing	Continuing
Radiation Injury Assessment and Therapeutic Approa/P505	9.119	8.875	8.680	8.921	9.130	9.289	9.423	Continuing	Continuing

(U) A. Mission Description and Budget Item Justification

(U) BRIEF DESCRIPTION OF ELEMENT

(U)This program supports applied research to investigate new approaches that will lead to advancements in biomedical strategies for preventing, treating, assessing and predicting the health effects of ionizing radiation, either alone or in combination with other biological warfare (BW)/chemical warfare (CW) toxicants. The premise is that DoD must be ready to conduct tactical, humanitarian or counterterrorism missions within radiation environments. Development of protective and therapeutic strategies will enable military forces to operate, when required, in nuclear or radioactive combat environments, while minimizing both short- and long-term risks of adverse health consequences. Advancements in tools to measure radiation exposure to military personnel will be used in triage, treatment decisions and risk assessment. Accurate models to predict casualties, particularly in combined nuclear-biological-chemical NBC environments, will promote effective command decisions and force structure planning to ensure mission success.
(U)The program has three primary goals: (1) to understand the pathological consequences of radiation injury and radiological hazards in order to provide a rational basis for prophylactic and therapeutic drug development; (2) to develop novel biological markers and delivery platforms for rapid, field-based individual dose assessment; (3) to define any interactions between radiation and BW or CW agents that cause more severe injury and the drugs used to protect against them -- with the goal of developing new models to predict casualties.
(U)The Armed Forces Radiobiology Research Institute (AFRRI), because of its multidisciplinary staff and facility resources, is uniquely qualified to execute the program prescribed by its mission. AFRRI`s radiation sources allow the simulation of any radiological environment that might be encountered. AFRRI is currently the sole laboratory with the combined capabilities needed to conduct this research.

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(U) Project Number and Title: P505 Radiation Injury Assessment and Therapeutic Approach

(U) PROGRAM ACCOMPLISHMENTS AND PLANS

(U) FY1999 Accomplishments:

(U) Identified new approaches for developing preventive treatments of both acute and chronic radiation injuries based on (a) applied knowledge of the fundamental mechanisms of cellular and molecular injury, (b) selection of novel, less toxic, but equally effective drugs, (c) pharmacologic quenching to reducing drug toxicity, and (d) new drug delivery alternatives.
($ 0.902 Million)
(U) Initiated studies to assess efficacy of conventional or slow-releasing radioprotectants to prevent or reduce late-arising health consequences of radiation injury, including cancer and chronic immune system suppression. ($ 0.972 Million)
(U) Established a high-throughput, *in vitro* gene array-based drug screening system to assess potential efficacy of pharmacologics for the prevention and treatment of radiation injury.
($ 0.790 Million)
(U) Demonstrated in an animal model efficacy against acute radiation-induced gastrointestinal tissue injury and associated infectious complications of a novel cytokine-based treatment regimen.
($ 0.650 Million)
(U) Designed, synthesized, and partially characterized two new classes of long-acting radioprotectants.
($ 0.772 Million)

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(U) Incorporated novel enhancements to a clinical radiation bioassay system under development that provides a rapid dose assessment capability for a broad spectrum of radiation qualities (gamma rays, x rays, and neutrons): Developed interphase cell-chromosome aberration bioassay that simplifies sample preparation in a standardized protocol that can be employed in clinical and reference laboratories by generalist laboratory technicians.
($ 0.798 Million)
(U) Demonstrated that two new classes of biological markers have the potential to significantly improve the accuracy and precision of measuring radiation doses in exposed individuals using polymerase chain reaction (PCR) bioassay systems that are rapid and easy to perform: (a) Confirmed dose-dependent increases in incidents of cells with mitochondrial DNA deletions after irradiation using a newly developed in situ PCR assay system; (b) Demonstrated inter-individual consistency of dose-related increase in oncogene expression after irradiation using a solution-based PCR procedure.
($ 0.779 Million)
(U) Completed additional studies extending the database of quantitative radiation/BW agent combined effects consequences for casualty prediction models: (a) Continued collecting useful data in studies assessing the effect of ionizing radiation on the protective immune status of individuals vaccinated against anthrax; (b) Initiated and began work under a collaborative agreement with USAMRIID to study the combined effects of radiation and Venezuelan equine encephalomyelitis (VEE) virus; and (c) Quantified the increased morbidity in an animal model system under a scenario involving radiation exposure of a population suffering from endemic shigellosis.
($ 1.225 Million)
(U)Completed assessment of the physiologic consequences (blood flow, body temperature, and motor activity) of combined exposure to radiation and the nerve agent prophylactic pyridostigmine.
($ 1.218 Million)
(U)Determined that DU induces morphologic changes (transforms) in human tissue culture cells that resemble the patterns seen tumor cells and that these transformed cells form tumors in immunologically-deficient rodents. Determined that elevated levels of oncogenes are expressed in tissues from rodents implanted with DU pellets. Continued pilot studies of immunotoxic and neurotoxic potential of DU. Continued research to improve sensitivity of a potentially-fieldable method to measure uranium in urine. Determined that tungsten induces a toxic response in cultured human cells.
($ 1.013 Million)

(U) FY2000 Plans:

(U) Continue to refine and test strategies for preventive treatments based on fundamental mechanisms of cellular and molecular injury and repair of blood-forming (hematopoietic) and gastrointestinal organ systems.
($ 1.700 Million)

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(U) Extend gene-based drug screening protocol to assessing efficacy of pharmacologics under both acute low-dose radiation exposures and/or chronic exposures.
($ 1.386 Million)
(U) Test efficacy of long-acting (slow-release) radioprotectants against acute radiation injury.
($ 1.000 Million)
(U)Continue development of clinical bioassays for assessment of radiation exposures: Automate sample preparations to reduce sample preparation times for cytogenetic-based assays and identify best-candidate bioassay procedure for assessing prior radiation exposure.
($ 0.721 Million)
(U) Continue development of molecular-based biological markers and analytical systems that can potentially produce highly accurate and rapid radiation dose assessments under field operations. Identify and calibrate biological markers that can both indicate total absorbed dose of radiation and differentiate whole-body from partial-body exposure. Incorporate the use of automated analytical systems to more efficiently and cost-effectively evaluate new candidate molecular biomarkers
($ 0.757 Million)
(U) Continue assessment of the effects of combined radiation and *B. anthracis* exposures on status of protective immunity. Quantify the biological interactions of radiation and non-lethal, incapacitating bacterial agents to provide data for incorporation into casualty prediction models of combined injuries. Extend radiation/BW agent interaction studies of viral threat agents to assess changes in mortality rates after combined exposure. Collate and analyze experimental data to improve and expand the predictive value of casualty prediction models and to provide information to improve clinical management of combined injuries. Complete assessment of treatment strategies for endemic shigellosis in irradiated animals.
($ 1.441 Million)
(U)Assess the combined effects of radiation exposure and sleep deprivation on brain wave patterns and sleep-wake cycle alterations.
($ 0.918 Million)
(U)Continue work on the carcinogenic potential of DU by initiating cancer marker and tumor development (life-span) studies in laboratory rodents. Continue studies in rodents on DU`s long-term effect on immune systems. Complete pilot study of tungsten toxicity.
($ 0.952 Million)

(U) FY2001 Plans:

(U) Continue to develop and test second-generation radioprotective treatments for sustained effectiveness efficacy. Assess efficacy of newly synthesized drug prototypes for protection against late-arising radiation injury.
($ 1.673 Million)
(U) Exploit gene-based drug screening protocols to assess the protective/therapeutic benefit of combining prophylactic and therapeutic regimens.
($ 1.324 Million)

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(U) Design simplified drug delivery systems for new drug prototypes: Commence initial design and testing of autoinjector systems, compounding alternatives for oral administration , and transdermal skin patches.
($ 1.015 Million)
(U)Continue development of clinical bioassays for assessment of radiation exposures. Automate sample preparations and reduce sample preparation times for cytogenetic biodosimetry test. Identify biological marker to differentiate prior from recent radiation exposures.($ 0.708 Million)
(U)Continue development of molecular biomarker systems for field use. Identify and calibrate biomarkers that can both indicate the amount of absorbed dose and differentiate whole-body from partial-body exposure. Develop automated analysis systems to efficiently evaluate promising candidate bioassays
($ 0.743 Million)
(U)Complete assessment of effectiveness of the anthrax vaccine to provide protection from infection following a combined radiation/*B.anthracis* exposure. Continue studies with other vaccines (e.g. for VEE) to assess effectiveness in combined radiation/infectious agent exposures. Continue and initiate studies to assess interaction of radiation and other infections resulting from BW agents.
($ 1.424 Million)
(U)Complete studies on the interaction of radiation and sleep deprivation on seizure incidence, brain waves and sleep-wake cycles.
($ 0.893 Million)
(U)Continue studies in laboratory rodents of cancer risk of DU and of long-term effects of exposure to DU on immune and nervous systems.
($ 0.900 Million)

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(U) B. Program Change Summary	**FY1999**	**FY2000**	**FY2001**	**Total Cost**
Previous President's Budget	9.212	8.903	8.742	Continuing
Appropriated Value	0.000	0.000	0.000	Continuing
Adjustments to Appropriated Value				
a. Congressionally Directed Undistributed Reduction	(.093)	0.000	0.000	
b. Rescission/Below-threshold Reprogramming, Inflation Adjustment	0.000	(.028)	(.062)	
c. Other	0.000	0.000	0.000	
Current President's Budget	9.119	8.875	8.680	Continuing

Change Summary Explanation:

(U) **Funding:** Funding changes are due to undistributed reductions, inflation savings and the government wide rescission.

(U) **Schedule:** N/A

(U) **Technical:** N/A

(U) **C.** **OTHER PROGRAM FUNDING SUMMARY COST:** N/A

(U) **D.** **ACQUISITION STRATEGY:** N/A

(U) **E.** **SCHEDULE PROFILE:** N/A